Practitioner's Docket No. U 015144-5 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re application of: Manne Satyanarayana REDDY, et al.
Serial No.: 10/822,154 Group No.: 1614
Filed: April 9, 2004 Examiner: -
For: CRYSTALLINE FORM III OF ANHYDROUS MOXIFLOXACIN HYDRO-CHLORIDE AND A PROCESS FOR PREPARATION THEREOF

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF CERTIFIED COPY

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country: INDIA

Application Number: 308/MAS/2003

Filing Date: APRIL 9, 2003

WARNING: "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

CERTIFICATE OF MAILING (37 C.F.R. 1.8a)

I hereby certify that this correspondence is, on the date shown below, being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Signature

Date: August 9, 2004

Janet I. Cord
(type or print name of person certifying)

SIGNATURE OF PRACTITIONER

Reg. No. 33778

JANET I. CORD
(type or print name of practitioner)

Tel. No.: (212) 708-1935

P.O. Address

Customer No.: 00140

c/o Ladas & Parry LLP
26 West 61st Street
New York, N.Y. 10023

NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification, Complete Specification, Abstract & Drawings of the extract of Patent Application No.308/MAS/2003, dated 09/04/2003 by Dr. Reddy's Laboratories Limited, having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 21st day of June 2004

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

CERTIFIED COPY OF
PRIORITY DOCUMENT

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018

Received Rs 5000/- in ~~Cash~~ Cheque/ ~~I.O./P.O./D.D.~~ on 09.04 Vide C.B.R. No. 5570.
914

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(Section 5(2), 7, 54 and 135 and Rule 33A)

1. I/We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016

2. (a) hereby declare that I am/ we are in possession of an invention titled **"Novel Crystalline Form-II of anhydrous 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro–1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid mono hydrochloride (Moxifloxacin hydrochloride) and a process for preparation there of.".**
   (b) that the Provisional/Complete specification relating to this invention is filed with this application.
   (c) that there is no lawful ground of objection to the grant of a patent to me/us.

3. further declare that the inventor(s) for the said invention is/are **Manne** Satyanarayana Reddy, Sajja Eswaraiah, Vetukuri Venkata Naga Kali Vara Prasada Raju, **Rapolu Rajesh,** and **Vedantham Ravindra** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500016, Andhra Pradesh.**

4. I/We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.

5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/patantee

6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on ____________________ under section 16 of the Act.

7. That I am/We are the assignee or legal representative of the true and first inventors.

8. That my/our address for service in India is as follows:

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:
I/We, the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

(Signed)_____
Manne Satyanarayana Reddy
H.No. 8-3-167/D/16,
Kalyan Nagar
Near AG Colony
Erragadda, Hyderabad-500 038

(Signed)_____
Sajja Eswaraiah.
LIG- 110,
Dharmareddy colony,
K.P.H.B.Colony
Hyderabad– 500 072.

(Signed)_____
Vetukuri Venkata Naga Kali Vara Prasada Raju
Flat No:404,Shiva durga Residency.
H.I.G: 216,217, VI Phase,
K.P.H.B. Colony,
Hyderabad-500 072.

(Signed)_____
Rapolu Rajesh Kumar
Post: Cherlapally,
Mandal & Dist: Nalgonda – 508 001.

(Signed) V. Ravi

Vedantham Ravindra.
S/O Vedantham Bhaskara Venkata
Narasimha Charyulu
D.No :28-1-80.
KANKARAGUNTA.
GUNTUR - 522004.

10. That to the best of ~~my~~/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to ~~me~~/us on this application.

11. Following are the attachments with the application
    (a) Provisional/Complete specification (---13--- pages, in triplicate)
    (b) Drawings (-05-- pages, in triplicate)
    (c) Priority documents(s)
    (d) Statement and Undertaking on Form-3.
    (e) Power of authority
    (f) Abstract of the invention (-02- page, in triplicate)
    (g) Fee Rs. 5000.00 (five thousand rupees only) in Cash/cheque/bank draft bearing No. dated drawn on HDFC Bank Limited, Lakdi-kapul, Hyderabad – 4.

I/We request that a patent may be granted to me/us for the said invention.

Dated this 31st day of March 2003.

(Signed) M. Satyanarayana Reddy

Dr. Manne Satyanarayana Reddy,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM-2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

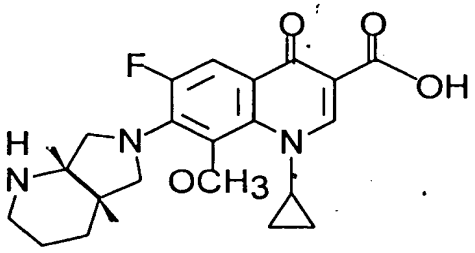
Novel Crystalline Form-II of anhydrous 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro -1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid mono hydrochloride (Moxifloxacin hydrochloride) and a process for preparation there of.

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to Novel Crystalline Form of anhydrous 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid mono hydrochloride, known under the generic name Moxifloxacin hydrochloride, Moxifloxacin hydrochloride can be depicted as Formula-(1).



. HCl .

• Formula- (1)

Moxifloxacin and its pharmaceutically acceptable salts are useful as antibiotics.

BACK GROUND OF THE INVENTION

The first generation of Quinolones includes Nalidixic acid was described as a first active substance by Lesher et, al, in 1962, (as Urinary tract antimicrobial agent), which was a by-product of chloroquine synthesis and thus a by-product of antimalaria research. Specially quinoline carboxylic acid derivatives constitute a class of extremely potent and orally active broad spectrum antibacterial agents. Several structural activity relationship (SAR) and quantitative structure activity relationship (QSAR) studies have led to the discovery of important class of Quinolines called fluoroquinolines.

Moxifloxacin Hydrochloride and its preparation described in EP-A-550903 and EP-A-591808.

USP 5,849,752 disclosed Moxifloxacin Hydrochloride monohydrate in the form of prismatic crystals having a characteristic peak at 168.1 ppm in the ^{13}C Solid state NMR spectrum and a band at 2θ =26.7(degrees) in the X-ray diffractogram along with their process for preparation and pharmaceutical formulations.

According USP 5,849,752, The Moxifloxacin Hydrochloride monohydrate in the form of prismatic crystals is characterized in that the anhydrous Moxifloxacin Hydrochloride is treated with an amount of water which is at least sufficient for thorough mixing and hydration until the stiochiometric content of water of crystallization has been absorbed for conversion of the crystal into monohydrate.

USP 5,849,752 has disclosed the anhydrous Moxifloxacin Hydrochloride, which is designated as Form-I for convenience by the inventors of the present invention and having XRD 2-theta values 5.8, 8.6, 10.3, 11.6, 13.6, 14.5, 15.0, 15.8, 17.3, 17.5, 18.3, 19.3, 19.6, 20.6, 21.5, 22.5, 22.8,23.0, 23.8,24.3, 24.7,25.0, 26.3, 27.0,27.4, 27.8,28.2, 29.4, 29.7, 30.0, 30.3, 31.3, 31.8, 34.5, 35.3, 37.1 degrees and having I.R. peaks at 722, 804, 834, 938, 957, 994, 1048, 1186, 1319, 1354, 1372, 1453, 1513, 1622, 1709, 2427, 2524, 2700, 2929, 3469 and 3527 cm^{-1}.

The latest trend that has crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the activity of different crystalline forms of a given drug. This has especially become very interesting after observing that many antibiotics, antibacterial, tranquillizers etc. exhibit polymorphism and some/one of the

crystalline forms of a given drug exhibit superior stability, bio-availability and consequently show much higher activity compared to other crystalline forms.

Hence, the novel crystalline form of anhydrous Moxifloxacin Hydrochloride the present invention is designated as Form-II of anhydrous Moxifloxacin Hydrochloride for convenience.

The process of the present invention is simple, non-hazardous and easily scalable for commercial production.

The Novel Anhydrous crystalline form of present invention is thermally stable, free flowing solid, non-solvated and readily suitable for pharmaceutical applications.

SUMMARY OF THE INVENTION.

The objective of the present invention is to provide novel crystalline Form of anhydrous Moxifloxacin Hydrochloride. This has been designated as Form-II for convenience.

The present invention also relates to the process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride which comprises, hydrolysis of Ethyl -1-cyclopropyl-6,7-difluoro –8-methoxy-1,4-dihydro-4-oxo quinoline –3-carboxylate in presence of a Hydrochloric acid to yield corresponding Quinoline carboxylic acid, which on further condensation with [S,S]-2,8-diazabicyclo-[4.3.0]nonane in an organic solvent such as DMSO, DMF, N-methyl pyrrolidinone, acetonitrile or pyridine etc., in the presence of acid binding agents such as alkali metal hydroxides, alkali metal carbonates, organic quinines or amides specially DABCO, DBU to produce Moxifloxacin.

Moxifloxacin is then treated with Hydrochloric acid to yield corresponding salt, which on further treatment with lower branched acid esters such as tertiary butyl acetate or an aliphatic hydrocarbon solvent such as cyclohexane or aromatic hydrocarbons such as

Toluene, and water is removed by Azeotropical reflux followed by conventional isolation to yield the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

The alternative route for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride comprises, dissolving Moxifloxacin hydrochloride in alcoholic solvents such as methanol at a temperature of 25-70 ^{O}C preferably at a temperature of 60-65 ^{O}C, followed by neutralization with anti solvent such as acetonitrile accompanied by gentle stirring for 10-24 hrs at a temperature of 25-35 ^{O}C. The resultant product is filtered and dried to yield the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride is characterized by X-ray diffractograms, IR spectrum, ^{13}C Solid State NMR, Thermal Gravimetric Analysis. and Differential Scanning Colorimetry.

The process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride of the present invention is commercially viable and well suitable for industrial scale up.

BREIF DESCRIPTION OF DRAWINGS

Fig.1 is characteristic X-ray powder diffractogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.2 is Infrared spectrum of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.3 is ^{13}C Solid State NMR, of novel crystalline polymorph Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.4 is Thermo gravimetric analysis thermogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.5 is Differential Scanning Colorimetry thermogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

The present invention related to novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride of Formula-(1) and a process for the preparation thereof.

The novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride of the present invention is characterized by its X-ray diffractograms, IR spectrum, ^{13}C Solid State NMR, Thermal Gravimetric Analysis. and Differential Scanning Colorimetry.

The anhydrous nature of the inventive substance was characterized by its thermo gravimetric analysis, and the anhydrous nature of the compound was also confirmed by calculating the water content present in the compound by Karl Fischer (KF) method.

The present inventive substance is having a moisture content of 0.20% by KF method, which confirms the anhydrous nature of the compound.

The X-ray powder diffraction pattern of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride has X-ray powder diffraction pattern essentially as shown in the Table-1. The X-ray powder diffraction pattern is expressed in terms of 2 theta (degrees).

Table-1:

2 theta (^{O})
5.691
7.109
8.450
8.771
10.022
10.235
10.457
11.418
12.180
13.108
13.992
14.406
14.744
15.081
15.522
16.528
17.154
17.700
18.478
19.191
19.661
20.306
21.550
22.173
23.017
23.559
24.029
24.578
25.034
25.727
26.406
27.249
27.846
28.279
28.907
29.861
32.233
34.894
35.924
36.619

37.298
39.057
41.246
41.761
44.594

The present invention of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride was characterized by its X-ray powder diffraction substantially as depicted in Figure (1).

The present invention provides the IR spectrum of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride substantially as depicted in Figure (2).

The present invention provides the Infrared data for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which was measured by KBr-transmission method with identified significant bands at about 651.43, 1027.03,1159.94 and 1733.75 cm^{-1}.

The present invention provides the ^{13}C-Solid state NMR spectra for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride substantially as depicted in Figure (3).

The present invention provides the ^{13}C-Solid state-NMR spectra for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which was recorded with a Bruker MSL 300 with characteristic peaks around at 107 ppm.

The present invention provides the thermo gravimetric analysis of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which is obtained from Shimadzu substantially and the relevant figure as depicted in Figure (4).

Further, present invention provides the Differential Scanning Calorimetry thermogram of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride substantially as depicted in Figure (5)

The present invention provides the Differential Scanning Calorimetry thermogram for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride exhibits a significant endo peak at 247.383^{O}C

Another embodiment of the present invention is to provide the preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which comprises;

i) refluxing azeotropically the reference sample of Moxifloxacin hydrochloride in lower branched or chained acid esters such as tertiary butyl acetate or an aliphatic hydrocarbon solvent such as cyclohexane or or aromatic hydrocarbons such as Toluene.

ii) cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;

iii) isolating the solid obtained in step (ii) by conventional methods;

iv) drying the isolated compound of step (iii) with or without vacuum at 30-100^{O}C, preferably 60-90^{O}C to afford novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

The alternative process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride which comprises;

i) dissolution of reference sample of Moxifloxacin hydrochloride in C1-C6 alcohols such as methanol at 25-70 ^{O}C preferably at 60-65 ^{O}C

ii) resultant solution mixture was precipitated with anti solvents such as acetonitrile in which product is poorly soluble;

iii) cooling the solution mixture of step (ii) accompanied by stirring of the mixture till the solid mass crystallizes;

iv) isolating the solid obtained in step (iii) by conventional methods;

v) drying the isolated compound of step (iv) with or without vacuum at 30-100°C, preferably 60-90°C to afford novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

Thus, the present invention is directed to a novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, with residual solvents within permissible limits, which renders it well suited for pharmaceutical formulations.

The present invention is described in detail with examples given below that are provided by the way of illustration only and therefore should not be construed to the limit scope of invention.

REFERENCE EXAMPLE:

Preparation of Moxifloxacin Hydrochloride:

1-cyclopropyl -6, 7-difluoro-1, 4-dihydro-4-oxo-8-methoxy quinolone-3-carboxylic acid (100 grams), (S,S) Diazabicyclo nonane (60 grams) and 1,8-Diazabicyclo[5.4.0.]undec-7-ene(DBU) (10.gms) were added to N-Methylpyrolidinone (250 ml) and the reaction mixture was slowly heated to the 60-70°C temperature and stirred till the reaction was substantially completed. 5% aqueous Isopropyl alcohol was added to the reaction mass, and pH was adjusted towards basic with caustic lye. Then the reaction mass was filtered. through clarifying filter, washed with 5% aqueous Isopropyl alcohol. Combined total filtrate and adjusted pH to 7.0 to 7.2 with Aqueous Hcl. and isolated at a temperature of 10-15°C to afford Moxifloxacin.

Moxifloxacin then treated with Hydrochloric acid in 10% aqueous methanol to yield corresponding hydrochloride salt.

(Wet weight: 115 gr.)

EXAMPLE – 1:

Preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride:

Moxifloxacin Hydrochloride (50 grams) (obtained from reference example) was suspended in tertiary butyl acetate (250 ml) and heated to reflux temperature of 90-100°C. Water was azeotropically removed, accompanied by cooling the reaction mixture to a temperature of 10-15°C under stirring for 30-60 mints to crystallize the solid mass. The crystallized mass was filtered, and washed with Tertiary butyl acetate (50 ml) and dried at a temperature of 60-70°C to afford the novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

(Weight: 46.8 grams, M.C. by KF is 0.20%)

EXAMPLE – 2:

Preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride :

Moxifloxacin Hydrochloride (115 grams) (obtained as per reference example) was dissolved in methanol (1000 ml) at reflux temperature accompanied by gently stirring for 30 min. Acetonitrile (1500 ml) was added to the above solution, the resultant solution was cooled to a temperature of 25-35°C and stirred for 21 hrs. The obtained solid mass was filtered and dried at a temperature of 50-70°C to afford the Novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

(Weight: 49 grams, M.C. by KF is 0.2%)

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig: 1 is characteristic X-ray powder diffraction pattern of the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

The significant 2 theta values (in degrees) obtained are 5.691,7.109, 8.450,8.771, 10.022, 10.235,10.457,11.418,12.180,13.108,13.992,14.406,14.744,15.081,15.522,16.528,17.154, 17.700,18.478,19.191,19.661,20.306,21.550,22.173,23.017,23.559,24.029,24.578,25.034, 25.727,26.406,27.249,27.846,28.279,28.907,29.861,32.233,34.894,35.924,36.619,37.298, 39.057,41.246,41.761,and 44.594 degrees two theta.

Fig: 2 is characteristic Infrared spectrum of novel crystalline polymorph Form-II of anhydrous Moxifloxacin Hydrochloride, with identified significant peaks at about 651.43, 1027.03,1159.94 and 1733.75 cm^{-1}.

Vertical axis: Wavelength (in Cm^{-1}); Horizontal axis: Transmission (in %).

Fig: 3 is characteristic ^{13}C-solid-NMR spectra of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which was recorded with a Bruker MSL 300. ^{13}C-solid-NMR spectra exhibits characteristic peaks around at 107 ppm

Fig: 4 is characteristic thermogram of thermogravimetric analysis of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride shows no significant weight loss at a temperature range of 0-250^{O}C indicates the anhydrous nature of the inventive substance of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

Vertical axis: weight of the compound (in mg); Horizontal axis: Temperature (in ^{O}C).

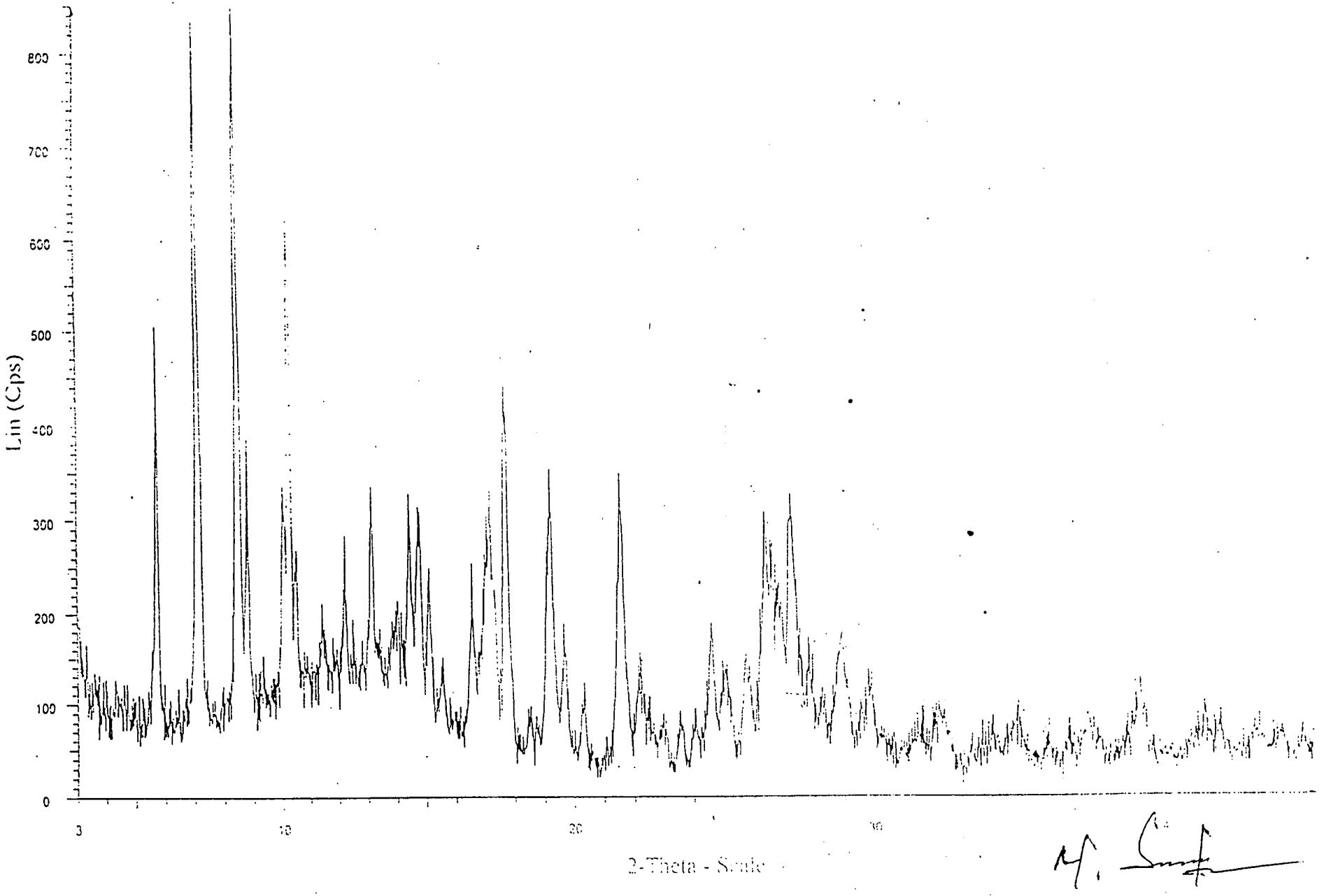
Fig: 5 is characteristic Differential Scanning Calorimetric thermogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride. The Differential Scanning Calorimetric thermogram exhibits a significant endo peak at 247.383°C.

Vertical axis: Temperature (in °C); Horizontal axis: Signal (in mV).

Dated 31st day of March, 2003

Signed)_____

Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.



MANNE SATYANARAYANA REDDY

Fig. 1

PERKIN ELMER

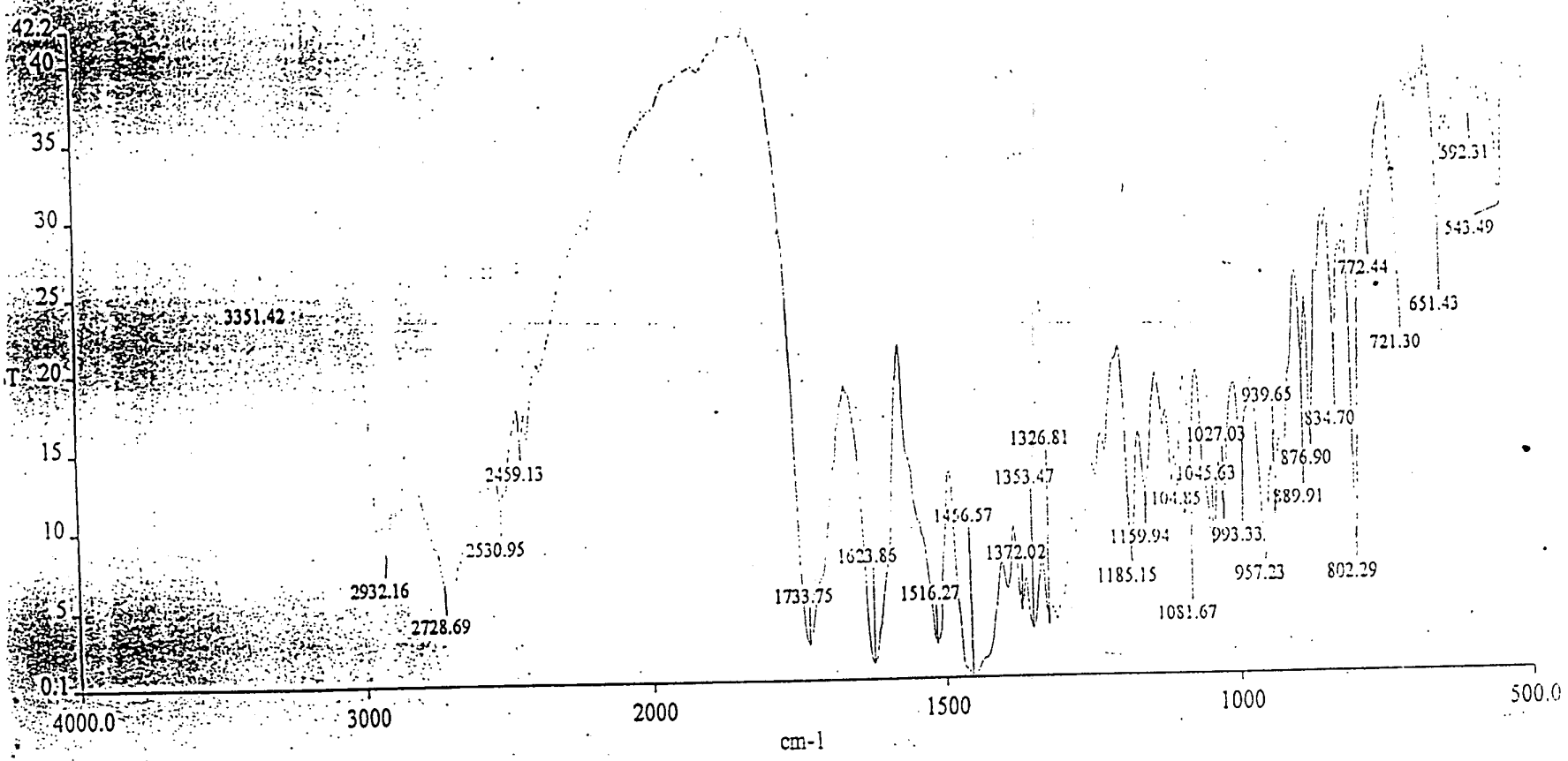


Fig. 2

MANNE SATYANARAYANA REDDY

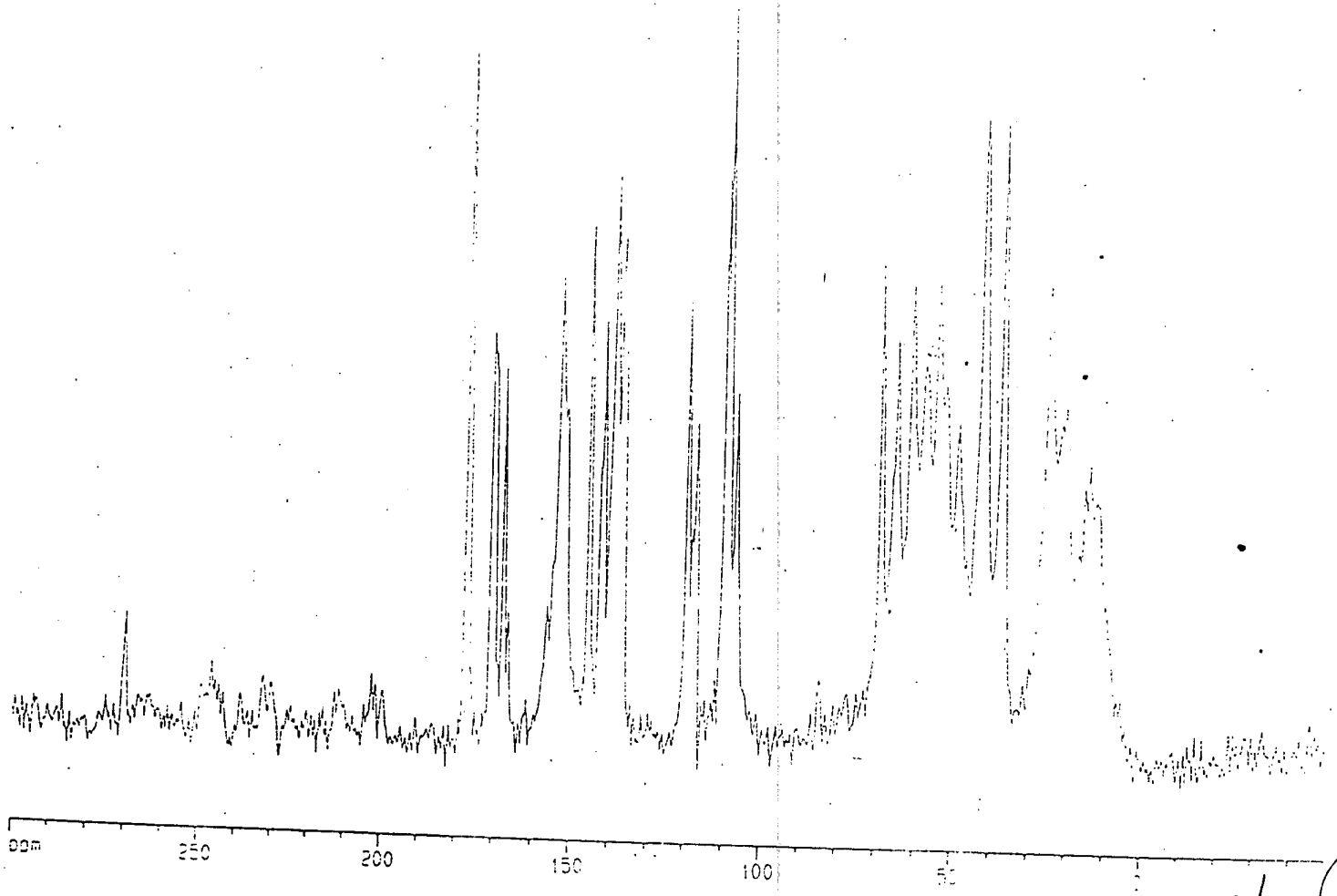


Fig. 3

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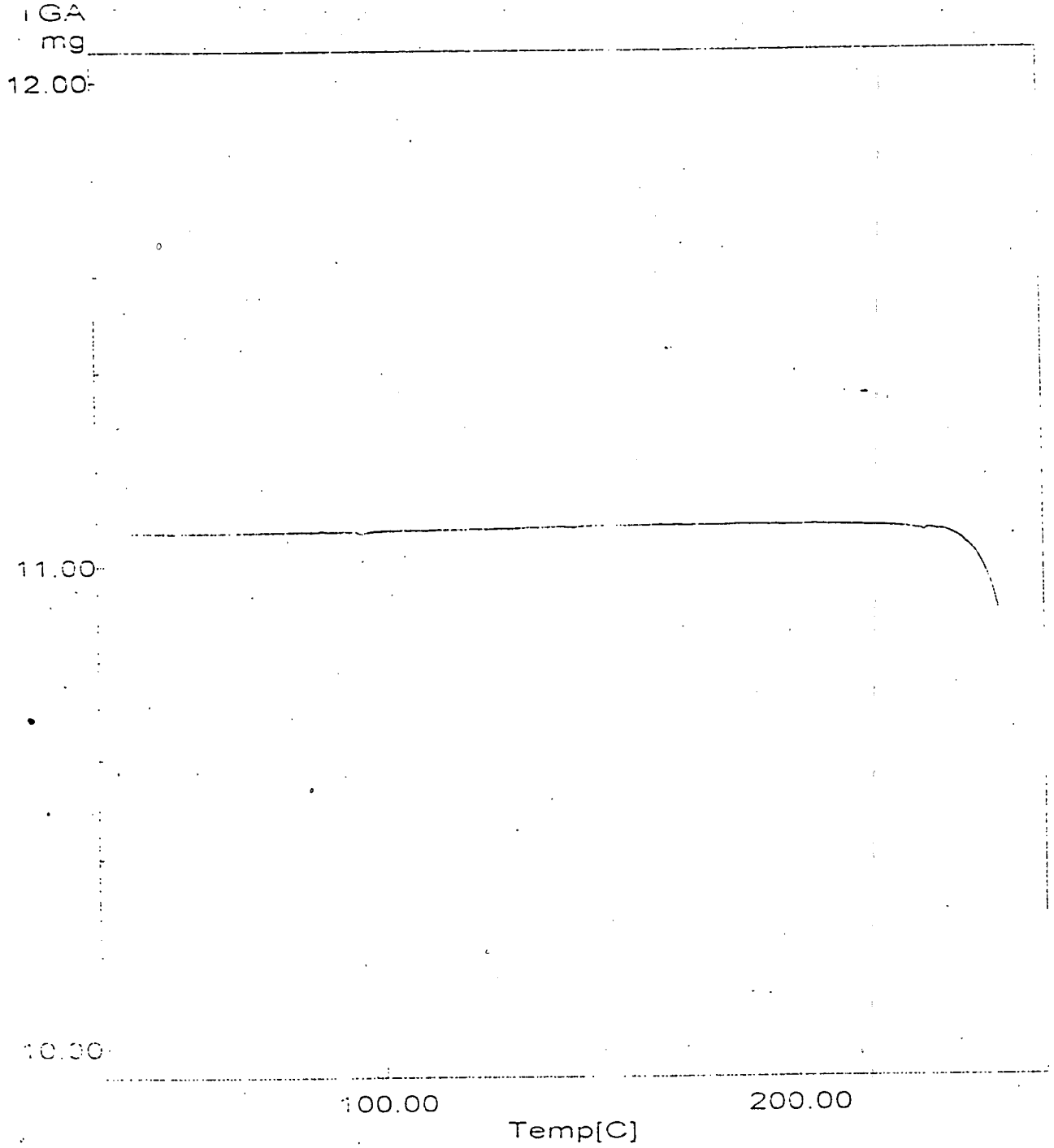


Fig. 4

MANNE SATYANARAYANA REDDY

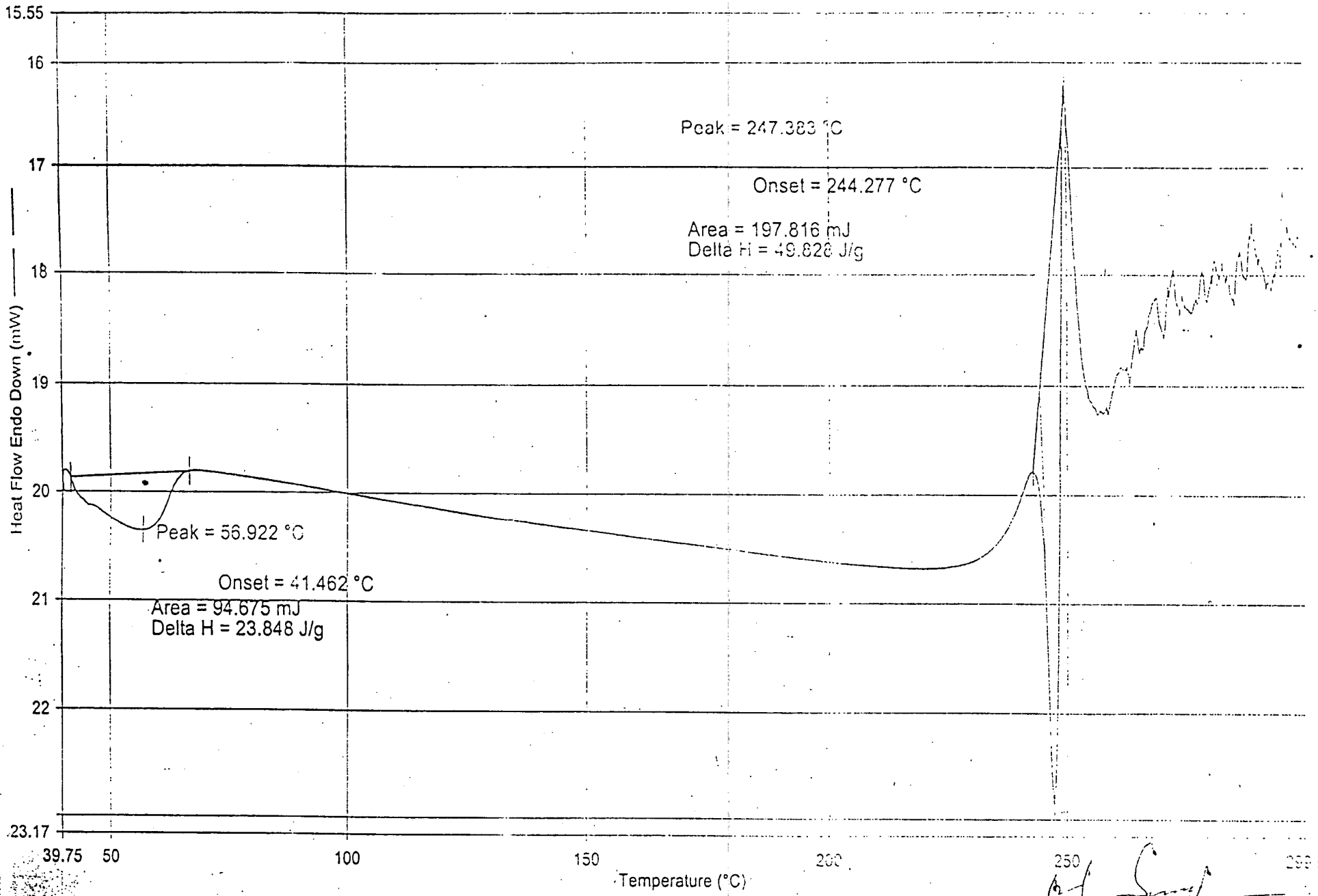


Fig. 5

MANNE SATYANARAYANA REDDY

FORM-A

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

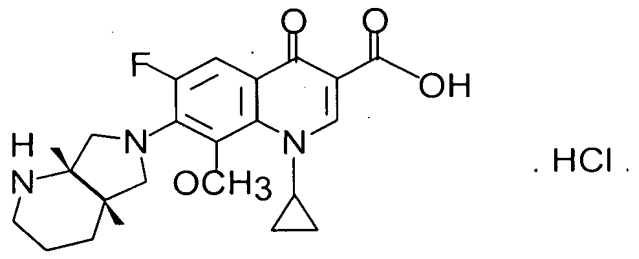
Novel Crystalline Form-II of anhydrous 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro -1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid mono hydrochloride (Moxifloxacin hydrochloride) and a process for preparation thereof.

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet,
Hyderabad-500 016, A.P., India.

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to Novel Anhydrous Crystalline Form of 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid - mono hydrochloride, known under the generic name Moxifloxacin hydrochloride, which can be depicted as Formula- (1).



Formula- (1)

Moxifloxacin and its pharmaceutically acceptable salts are useful as antibiotics.

BACK GROUND OF THE INVENTION

The first generation of Quinolones includes Nalidixic acid was described as a first active substance by Lesher et..al,in 1962,(as Urinary tract antimicrobial agent),which was a by-product of chloroquine synthesis and thus a by-product of antimalaria research.

Specially quinoline carboxylic acid derivatives constitute a class of extremely potent and orally active broad spectrum antibacterial agents. Several structural activity relationship (SAR) and quantitative structure activity relationship

(QSAR) studies have led to the discovery of important class of Quinolines called fluoroquinolines.

Moxifloxacin Hydrochloride and its preparation described in EP-A-550903 and EP-A-591808.

USP 5,849,752 disclosed Moxifloxacin Hydrochloride monohydrate in the form of prismatic crystals having a characteristic peak at 168.1 ppm in the ^{13}C Solid state NMR spectrum and a band at 2θ =26.7(degrees) in the X-ray diffractogram along with their process for preparation and pharmaceutical formulations.

According USP 5,849,752, The Moxifloxacin Hydrochloride monohydrate in the form of prismatic crystals is characterized in that the anhydrous Moxifloxacin Hydrochloride is treated with an amount of water which is at least sufficient for thorough mixing and hydration until the stiochiometric content of water of crystallization has been absorbed for conversion of the crystal into monohydrate.

USP 5,849,752 has disclosed the anhydrous Moxifloxacin Hydrochloride, which is designated as Form-I for convenience by the inventors of the present invention and having XRD 2-theta values 5.8, 8.6, 10.3, 11.6, 13.6, 14.5, 15.0, 15.8, 17.3, 17.5, 18.3, 19.3, 19.6, 20.6, 21.5, 22.5, 22.8,23.0, 23.8,24.3, 24.7,25.0, 26.3, 27.0,27.4, 27.8,28.2, 29.4, 29.7, 30.0, 30.3, 31.3, 31.8, 34.5, 35.3, 37.1 degrees and having I.R. peaks at 722, 804, 834, 938, 957, 994, 1048, 1186, 1319, 1354, 1372, 1453, 1513, 1622, 1709, 2427, 2524, 2700, 2929, 3469 and 3527 cm^{-1}.

The latest trend that has crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the activity of different crystalline forms of a given drug. This has especially become very interesting after observing that many antibiotics, antibacterial, tranquillizers etc. exhibit polymorphism and some/one of the

crystalline forms of a given drug exhibit superior stability, bio-availability and consequently show much higher activity compared to other crystalline forms.

Nevertheless, new crystalline form of anhydrous Moxifloxacin Hydrochloride and methods of making new crystalline form of anhydrous Moxifloxacin Hydrochloride are desirable.

SUMMARY OF THE INVENTION.

In accordance with one aspect, the invention provides a new crystalline Form of anhydrous Moxifloxacin Hydrochloride. This has been designated as Form-II for convenience.

In accordance with another aspect, the invention provides the process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride which comprises, hydrolysis of Ethyl -1-cyclopropyl-6,7-difluoro –8-methoxy-1,4-dihydro-4-oxo quinoline –3-carboxylate in presence of a Hydrochloric acid to yield corresponding Quinoline carboxylic acid, which on further condensation with [S,S]-2,8-diazabicyclo-[4.3.0]nonane in an organic solvent such as DMSO, DMF, N-methyl pyrrolidinone, acetonitrile or pyridine etc., in the presence of an acid binding agents such as alkali metal hydroxides, alkali metal carbonates, organic quinines or amides specially DABCO, DBU to produce Moxifloxacin.

Moxifloxacin is then treated with hydrochloric acid to yield corresponding salt, which on further treatment with lower branched acid esters such as tertiary butyl acetate or an aliphatic hydrocarbon solvent such as cyclohexane or aromatic hydrocarbons such as toluene or aliphatic ketones such as methylisobutylketone, and water is removed by

azeotropical reflux followed by conventional isolation to yield the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

In accordance with another aspect, the invention also provides the alternative route for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride comprises, dissolving Moxifloxacin hydrochloride in alcoholic solvents such as methanol at a temperature of 25-70 ^{O}C preferably at a temperature of 60-65 ^{O}C, followed by neutralization with anti solvent such as acetonitrile accompanied by gentle stirring for 10-24 hrs at a temperature of 25-35 ^{O}C. The resultant product is filtered and dried to yield the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride. The process of the present invention is simple, non-hazardous and easily scalable for commercial production.

The novel anhydrous crystalline form of present invention is thermally stable, highly pure, free flowing solid, non-solvated and readily suitable for pharmaceutical applications.

Novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride is characterized by X-ray diffractograms, IR spectrum, ^{13}C Solid State NMR, Thermal Gravimetric Analysis. and Differential Scanning Colorimetry.

BREIF DESCRIPTION OF DRAWINGS

Fig.1 consists of characteristic X-ray powder diffractogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.2 consists of Infrared spectrum of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.3 consists of ^{13}C Solid State NMR, of novel crystalline polymorph Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.4 consists of Thermogravimetric analysis thermogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Fig.5 consists of Differential Scanning Colorimetry thermogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride of Formula-(1) and a process for the preparation thereof.

The novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride of the present invention is characterized by its X-ray diffractograms, IR spectrum, ^{13C} Solid State NMR, Thermal Gravimetric Analysis. and Differential Scanning Colorimetry.

The anhydrous nature of the inventive substance was characterized by its thermo gravimetric analysis, and was also confirmed by calculating the water content present in the compound by Karl Fischer (KF) method.

The present inventive substance is having moisture content equal to or less than 0.60% by KF method. The present invention also provides the thermogravimetric analysis of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, characteristic thermogram of thermo gravimetric analysis of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride shows no significant percent weight change from 0-150^{O}C. This tends to demonstrate that novel crystalline Form-II of Moxifloxacin hydrochloride is thus anhydrous.

The TGA thermogram was obtained from Shimadzu TGA-50 and the relevant figure as depicted in Figure (4).

The novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride has X-ray powder diffraction pattern essentially as shown in the Table-1. The X-ray powder diffraction pattern is expressed in terms of 2 theta (degrees).

Table-1:

2 theta (^{O})
5.6
7.1
8.4
8.8
10.0
10.4
11.4
12.2
13.1
13.9
14.4
14.7
16.6
16.9
17.2
17.7
18.5
19.1
19.2
19.8
20.1
20.3
21.1
21.5
22.1
22.6
22.9
23.5
24.0
24.6
24.9
25.8
26.2
26.6

26.9
27.2
28.7
29.1
29.7
30.1
31.4
32.1
37.3
39.0
40.8
41.5
42.2
43.1

The present invention of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride was characterized by its X-ray powder diffraction substantially as depicted in Figure (1).

The X-ray powder diffraction pattern of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The present invention provides the Infrared data for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which was measured by KBr-transmission method with identified significant bands at about 1159.38 and 2706.71 cm^{-1}. The present invention provides the IR spectrum of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride was recorded with Perkin Elmer and substantially as depicted in Figure (2).

The present invention provides the ^{13}C-Solid state-NMR spectra for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which was recorded with a Bruker MSL 300 with characteristic signal at around 107 ppm. The present invention provides

the ^{13}C-Solid state NMR spectra for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride substantially as depicted in Figure (3).

The present invention provides the Differential Scanning Calorimetry thermogram for novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride exhibits a significant endo peak at 246.440^{O}C. The present invention provides the Differential Scanning Calorimetry thermogram of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride was recorded on Perkin- Elmer Pyris 6 DSC substantially as depicted in Figure (5).

Another embodiment of the present invention is to provide the preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which comprises;

i) refluxing azeotropically Moxifloxacin hydrochloride (obtained form reference example) in lower branched or chained acid esters such as tertiary butyl acetate or an aliphatic hydrocarbon solvent such as cyclohexane or aromatic hydrocarbons such as toluene or aliphatic ketones such as methylisobutylketone,

ii) cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;

iii) isolating the solid obtained in step (ii) by conventional methods;

iv) drying the isolated compound of step (iii) with or without vacuum at 30-100^{O}C, preferably 60-90^{O}C to afford novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

The alternative process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride which comprises;

i) dissolution of Moxifloxacin hydrochloride (obtained form reference example) in C1-C6 alcohols such as methanol at 25-70 ^{O}C preferably at 60-65 ^{O}C

ii) resultant solution mixture was precipitated with anti solvents such as acetonitrile in which product is poorly soluble;

iii) cooling the solution mixture of step (ii) accompanied by stirring of the mixture till the solid mass crystallizes;

iv) isolating the solid obtained in step (iii) by conventional methods;

v) drying the isolated compound of step (iv) with or without vacuum at 30-100^{O}C, preferably 60-90^{O}C to afford novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

The present invention is based on the surprising recognition that a highly pure novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride is obtained which purity about 99.9%, as measured by HPLC.

Thus, the present invention is directed to a novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, with residual solvents within permissible limits, which renders it well suited for pharmaceutical formulations.

The present invention is described in detail with examples given below that are provided by the way of illustration only and therefore should not be construed to the limit scope of invention.

REFERENCE EXAMPLE:

Preparation of Moxifloxacin Hydrochloride:

1-cyclopropyl -6, 7-difluoro-1, 4-dihydro-4-oxo-8-methoxy quinolone-3-carboxylic acid (100 grams), (S,S) Diazabicyclo nonane (60 grams) and 1,8-Diazabicyclo[5.4.0.]undec-7-ene(DBU) (10.gms) were added to N-Methylpyrolidinone (250 ml) and the reaction mixture was slowly heated to the 60-70°C temperature and stirred till the reaction was substantially completed. 5% aqueous isopropyl alcohol was added to the reaction mass, and pH was adjusted towards basic with caustic lye. Then the reaction mass was filtered. through clarifying filter, washed with 5% aqueous isopropyl alcohol. Combined total filtrate and adjusted pH to 7.0 to 7.2 with aqueous Hcl. and isolated at a temperature of 10-15°C to afford Moxifloxacin.

Moxifloxacin then treated with Hydrochloric acid in 10% aqueous methanol to yield corresponding hydrochloride salt.

(Wet weight: 115 grams)

EXAMPLE – 1:

Preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride:

Moxifloxacin Hydrochloride (50 grams) (obtained from reference example) was suspended in tertiary butyl acetate (250 ml) and heated to reflux temperature of 90-100°C. Water was azeotropically removed, accompanied by cooling the reaction mixture to a temperature of 10-15°C under stirring for 30-60 mints to crystallize the solid mass. The crystallized mass was filtered, and washed with tertiary butyl acetate (50 ml) and dried at a temperature of 60-70°C to afford the novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

(Weight: 46.8 grams, M.C. by KF is 0.20%)

EXAMPLE – 2:

Preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride :

Moxifloxacin Hydrochloride (115 grams) (obtained as per reference example) was dissolved in methanol (1000 ml) at reflux temperature accompanied by gently stirring for 30 min. Acetonitrile (1500 ml) was added to the above solution, the resultant solution was cooled to a temperature of 25-35°C and stirred for 21 hrs. The obtained solid mass was filtered and dried at a temperature of 50-70°C to afford the Novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

(Weight: 49 grams, M.C. by KF is 0.2%)

EXAMPLE – 3:

Preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride :

Moxifloxacin Hydrochloride (40 grams) (obtained from reference example) was suspended in methyl isobutyl ketone (400 ml) and heated to 110-120°C, while collecting the low boilers and refluxed azeotropically between 115-120°C and then reaction mass is cooled to 25-35°C and product is filtered and dried at 80-90°C under vacuum to afford the novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

(Weight: 35.8gms, M.C. by KF is 0.20%; Purity by HPLC: 99.88%).

EXAMPLE – 4:

Preparation of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride :

1-cyclopropyl -6, 7-difluoro-1, 4-dihydro-4-oxo-8-methoxy quinolone-3-carboxylic acid (50 Kgs), (S,S) diazabicyclo nonane (1.49 equivalents) and 1,8-diazabicyclo [5.4.0.] undec-7-ene(DBU) (5Kgs) were added to N-methylpyrolidinone (125L) in SS Reactor and the reaction mixture was slowly heated to the 60-65°C temperature and stirred till the reaction was substantially completed. 500L of 5% aqueous isopropyl alcohol was added

to the reaction mass, and pH was adjusted to 5.0-6.0 and the product is isolated at 20-25°C.Wet cake is recrystallised in aqueous methanol at pH1.5-2.0,and is made slurry in 5% aqueous methanol. Then wet cake was dissolved in aqueous methanol and the reaction mass was filtered through clarifying filter, washed with aqueous methanol. Combined total filtrate pH was adjusted to 1.5-2.0 with Aqueous Hcl.

Finally, wet cake is taken with methyl isobutylketone (800ml) and heated to reflux while collecting the low boilers and refluxed azeotropically between 115-120°C and then reaction mass is cooled to 25-35°C and product is filtered and dried at 80-90°C under vacuum to afford the novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride. (Weight: 31.3Kgs, M.C. by KF is 0.60%; Purity by HPLC: 99.94%).

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig: 1 consist of characteristic X-ray powder diffraction pattern of the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

The significant 2 theta values (in degrees) obtained are 5.6,7.1,8.4,8.8, 10.0,10.4, 11.4,12.2,13.1,13.9,14.4,17.7,16.6,16.9,17.2,17.7,18.5,19.1,19.2,19.8, 20.1,20.3,21.1,21.5,22.1,22.6,22.9,23.5,24.0,24.6,24.9,25.8,26.2,26.6, 26.9,27.2,28.7,29.1,29.7,30.1,31.4,32.1,37.3,39.0 and 40.8 degrees two theta.

Fig: 2 consist of characteristic Infrared spectrum of novel crystalline polymorph Form-II of anhydrous Moxifloxacin Hydrochloride, with identified significant bands at about 1159 and 2706.71 cm^{-1}.

Vertical axis: Wavelength (in Cm^{-1}); Horizontal axis: Transmission (in %).

Fig: 3 consist of characteristic ^{13}C-solid-NMR spectra of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride, which was recorded with a Bruker MSL 300. ^{13}C-solid-NMR spectra exhibits characteristic peaks around at 107 ppm.

Fig: 4 consist of characteristic thermogram of thermogravimetric analysis of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride shows no significant percent weight change from 0-150^{O}C indicates the anhydrous nature of the inventive substance of novel crystalline Form-II of anhydrous Moxifloxacin hydrochloride.

Vertical axis: weight of the compound (in mg); Horizontal axis: Temperature (in ^{O}C).

Fig: 5 consist of characteristic Differential Scanning Calorimetric thermogram of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride. The Differential Scanning Calorimetric thermogram exhibits a significant endo peak at 246.440^{O}C.

Vertical axis: Temperature (in ^{O}C); Horizontal axis: Signal (in mV).

We Claim:

Novel anhydrous crystalline Form-II of 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid mono hydrochloride (Moxifloxacin hydrochloride).

The novel anhydrous crystalline Form- II of Moxifloxacin hydrochloride of claim 1 having X-ray powder diffraction pattern with characteristic peaks around 7.1, 8.8, 10.4, 12.2,13.9,14.7,17.7 and 21.5 two-theta degrees.

The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1; which provides X-ray diffraction pattern substantially in accordance with Figure (1).

The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1, having an identified characteristic Infrared bands around 1159 and 2706 cm^{-1}.

The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 4,having an Infrared spectrum substantially in accordance with Figure (2).

6. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1, having an identified characteristic signal in ^{13}C-solid state NMR at around 107 ppm.
7. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 6,having ^{13}C-solid state-NMR spectrum substantially in accordance with Figure (3).

8. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1, having no significant percent weight change from 0-150^{O}C in thermogram of thermogravimetric analysis.

9. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 8, having Thermogram substantially in accordance with Figure (4).

10. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1, having the moisture content about 3.0% or less than 3.0%.

11. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1 is substantially pure.

12. The novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride according to claim 1, having the purity greater than 99.6% by HPLC.

13. A process for preparing the novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride, which comprises;

    i) refluxing azeotropically Moxifloxacin hydrochloride (obtained form reference example) in lower branched or chained acid esters such as tertiary butyl acetate or an aliphatic hydrocarbon solvent such as cyclohexane or and aromatic hydrocarbons such as Toluene, or Aliphatic ketones such as Methylisobutylketone, or

    dissolution of Moxifloxacin hydrochloride (obtained form reference example) in C1-C6 alcohols such as methanol at 25-70 ^{O}C preferably at 60-65 ^{O}C and neutralization with anti solvents like acetonitrile in which product is poorly soluble;

ii) cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;

iii) isolating the solid obtained in step (ii) by conventional methods;

iv) drying of the isolated compound of step (vii) with / without vacuum at 30-100°C, preferably 60-90°C to afford anhydrous crystalline polymorph form-II of Moxifloxcin hydrochloride.

14. The process according to step (i) of claim 12, wherein the preferable solvents are tetrabutyl acetate, methyl isobutylketone, methanol and acetonitrile.

15. The process for the preparation of novel anhydrous crystalline Form-II of Moxifloxacin hydrochloride is substantially as herein described and exemplified.

Dated 20th day of February, 2004

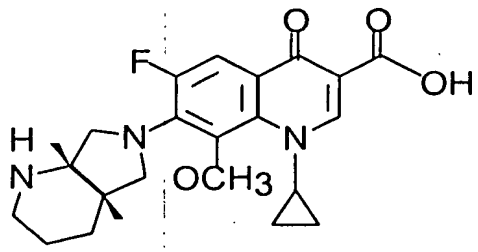
Signed) S. Venkataraman

Mr.Sunderam Venkatraman,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.

ABSTRACT

Title of the Invention: Novel Crystalline Form-II of anhydrous 1-cyclopropyl -7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro -1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid mono hydrochloride (Moxifloxacin hydrochloride) and a process for preparation there of.

The objective of the present invention is to provide novel crystalline Form of anhydrous Moxifloxacin Hydrochloride. This has been designated as Form-II for convenience. Moxifloxacin Hydrochloride can be depicted as Formula-(1).



. HCl .

Formula- (1)

The present invention also relates to the process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride which comprises, hydrolysis of Ethyl -1-cyclopropyl-6,7-difluoro –8-methoxy-1,4-dihydro-4-oxo quinoline –3-carboxylate in presence of a Hydrochloric acid to yield corresponding Quinoline carboxylic acid, which on further condensation with [S,S]-2,8-diazabicyclo-[4.3.0]nonane in an organic solvent such as DMSO, DMF, N-methyl pyrrolidinone, acetonitrile or pyridine etc., in the presence of acid binding agents such as alkali metal hydroxides, alkali metal carbonates, organic quinines or amides specially DABCO, DBU to produce Moxifloxacin.

Moxifloxacin is then treated with Hydrochloric acid to yield corresponding salt, which on further treatment with lower branched acid esters such as tertiary butyl acetate or an

aliphatic hydrocarbon solvent such as cyclohexane or aromatic hydrocarbons such as Toluene, and water is removed by Azeotropical reflux followed by conventional isolation to yield the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

The alternative route for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride comprises, dissolving Moxifloxacin hydrochloride in alcoholic solvents such as methanol at a temperature of 25-70 ^{O}C preferably at a temperature of 60-65 ^{O}C, followed by neutralization with anti solvent such as acetonitrile accompanied by gentle stirring for 10-24 hrs at a temperature of 25-35 ^{O}C. The resultant product is filtered and dried to yield the novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride.

The process for the preparation of novel crystalline Form-II of anhydrous Moxifloxacin Hydrochloride of the present invention is commercially viable and well suitable for industrial scale up.

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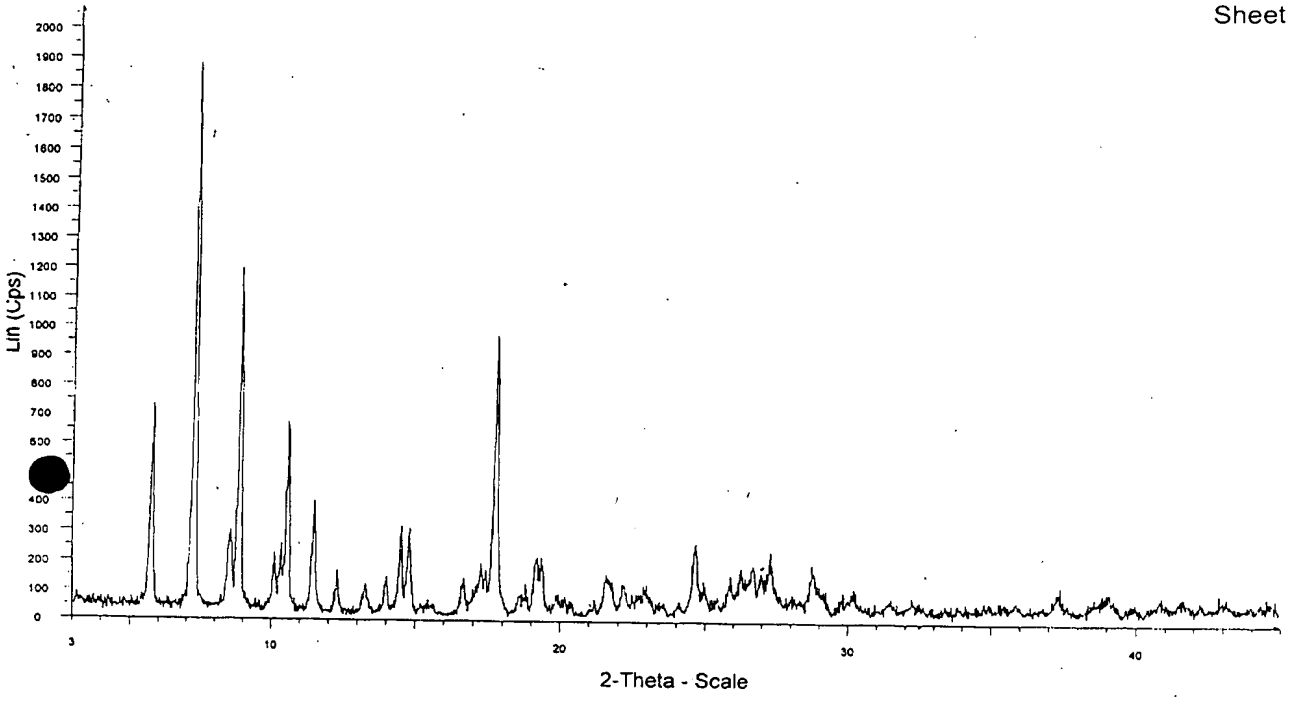

Fig. 1

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MF 005H03, 13C cpmas
at 5KHz

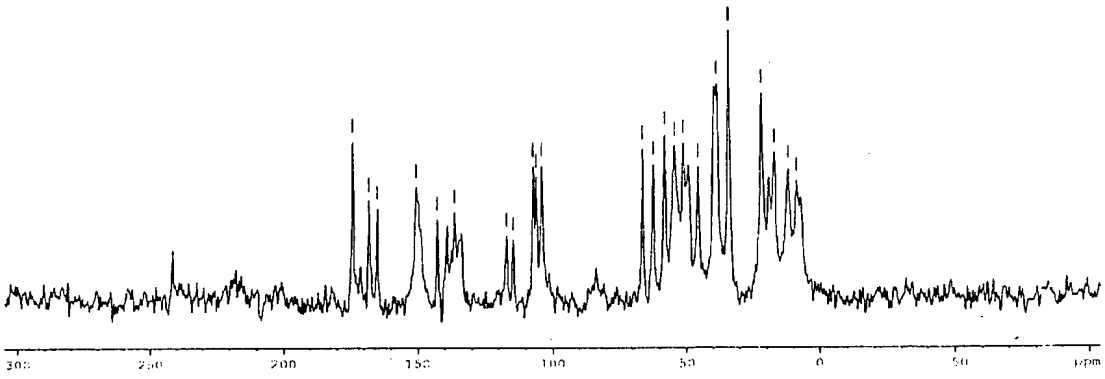

Fig. 2

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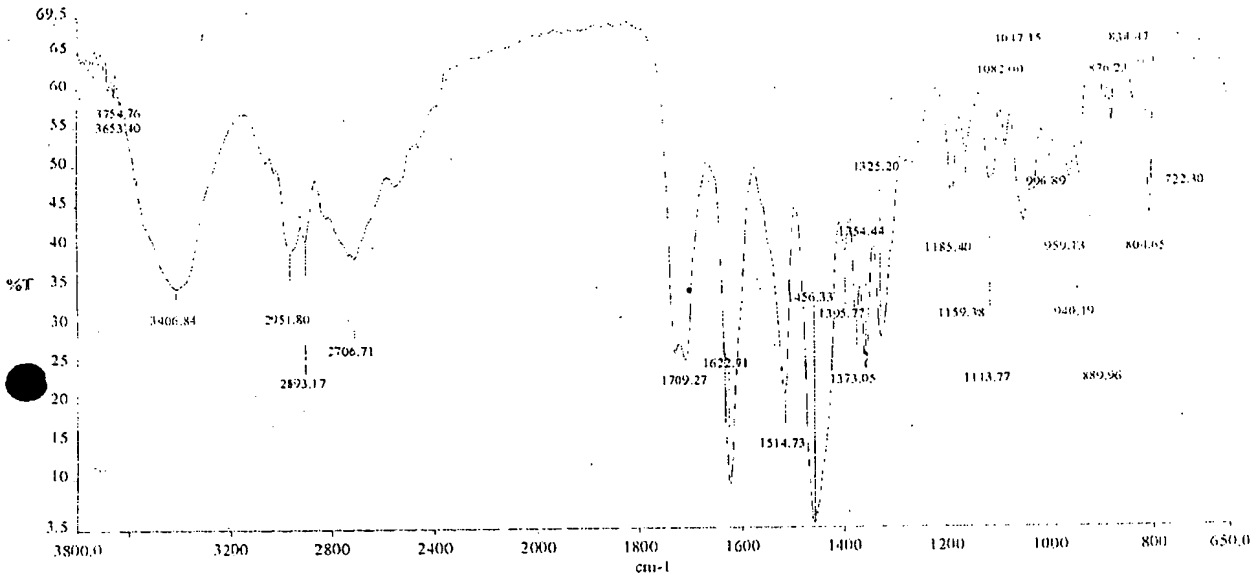

Fig. 3

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Thermal Analysis Data

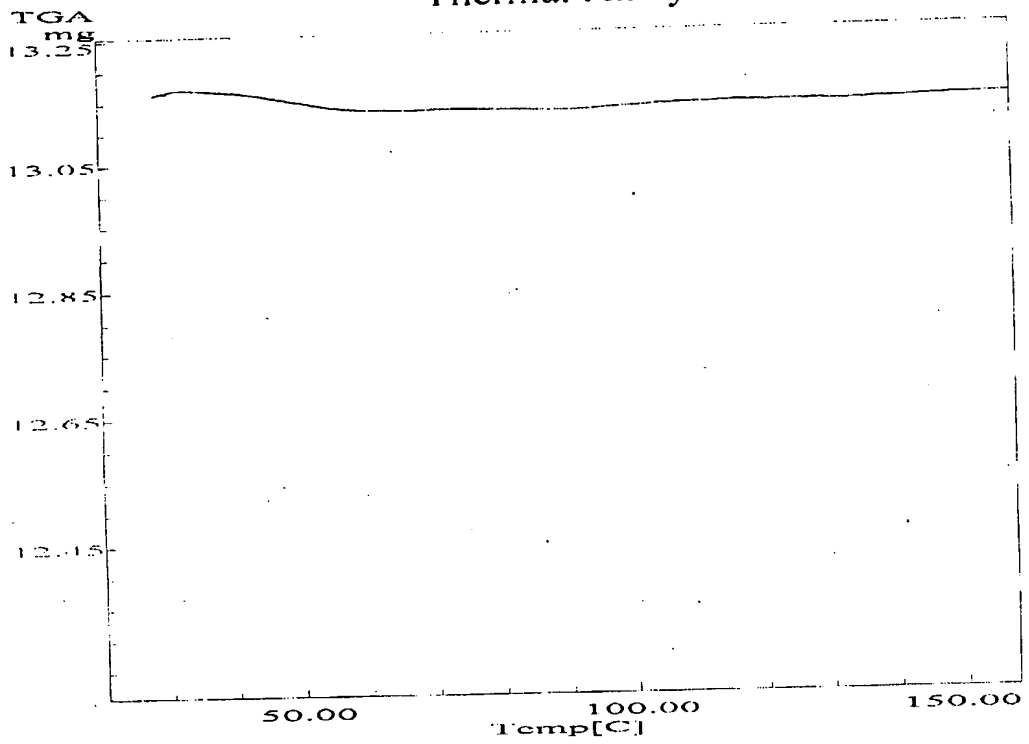

Fig. 4

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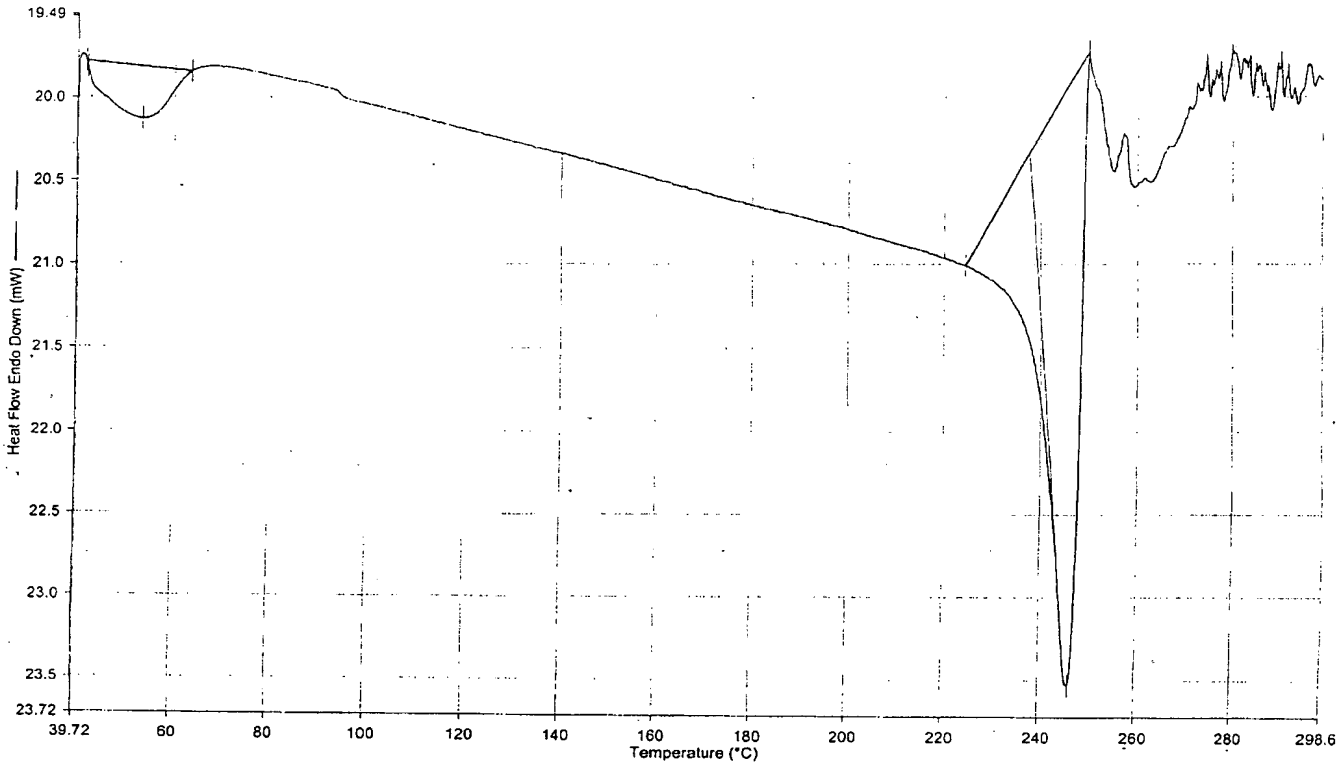

Fig. 5

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